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ORIGINAL PAPERS

Impact of the age of diagnosis on the natural history of ulcerative colitis

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ABSTRACT

Background: Ulcerative colitis (UC) has a recognized phenotypic heterogeneity. Some studies suggest that age at diagnosis may influence features and natural history of the disease.

Aim: This study aimed to compare patients', disease's and treatment's features between Portuguese patients diagnosed before and after the age of 40-years-old.

Methods: Retrospective single-center study that included 310 patients with UC, divided in two groups: Those diagnosed before the age of 40-years-old (early onset UC) and those diagnosed later than that (late onset UC). In each group features of the patients (gender, family history, smoking), of the disease (duration, extension, severity, clinical course, hospitalization, extraintestinal manifestations), and of treatment (oral aminosalicylates, systemic steroids or immunomodulators) were analyzed. Statistical analysis was performed using SPSSv22.0. Univariate and multivariate analyses were performed to assess factors associated with early and late onset UC.

Results: From the analyzed patients, 207 had UC diagnosed before the age of 40 years old (43.5% men; mean age at diagnosis 29.4 ± 6.9 years) and 103 were diagnosed after that age (61.2% men; mean age at diagnosis 51.8 ± 8.1 years). In the group diagnosed before 40 years old, female gender (p = 0.003), severe disease (p = 0.002), chronic intermittent clinical course (p = 0.026), and hospitalizations (p = 0.001) were significantly more frequent. The use of oral aminosalicylates (p = 0.032), systemic steroids (p = 0.003) and immunomodulators (p = 0.012) were also more common in the early onset UC group. No differences between groups were found in family history, smoking, disease's extension, extraintestinal manifestations, and use of biological agents. Multivariate analysis pointed early onset UC to be significantly associated with female gender (odds ratio [OR], 1.77; 95% confidence interval [CI], 1.08-2.91; p = 0.024), chronic intermittent symptoms (OR, 2.34; 95% CI, 1.17-4.70; p = 0.016), and need of hospitalization (OR, 2.89; 95% CI, 1.46-5.72; p = 0.002).

Conclusions: When diagnosed before the age of 40-years-old, UC preferably affects women and manifests as a more severe disease, with more frequent hospitalizations and chronic intermittent symptoms. These facts might have implications in planning timely and individualized future therapeutic strategies.

Key words: Ulcerative colitis. Age of diagnosis. Onset. Natural history.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that is believed to result from the combination of genetic factors, environmental exposures, and atypical immune responses to the gut microbiota (1). Although previously reported to occur according to a north-south gradient in Europe (2), the prevalence of UC in Southern European countries, namely in Portugal, seems to be increasing, reaching in some studies comparable values of those found in northern Europe countries (3,4). The estimated prevalence of UC in the Portuguese population was 71 per 100,000 in 2007 (4).

The onset of UC occurs mainly in younger individuals, usually in the third or fourth decade of life (5,6). However, it is currently well described a bimodal distribution of disease onset with a minor second peak arising in older patients (7,8). As the world's population is ageing, it is not unexpected that the number of patients receiving a diagnostic of UC later in life will soon increase. In what way this group of patients differs from those patients diagnosed earlier in life is still matter of debate. Certain older studies suggested that patients with a late onset UC had a less extensive disease but with a more aggressive clinical course, requiring steroids and hospitalizations more frequently (9,10). Conversely, other more recent reports pointed that late onset UC may have a more benign clinical course (11,12).

There is no doubt that UC remains a heterogeneous disease in which a specific clinical course is difficult to pre-

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dict. For this reason, the identification of certain individual and unambiguous factors at the moment of diagnosis may help in optimizing medical therapies, as well as in establishing a more accurate disease's prognostic.

The aim of this study was to identify differences between patients with early onset and late onset UC, namely among patients' characteristics, disease's features, and therapeutic requirements, in a northern Portuguese population. As far as is known, this is the first published Portuguese study specifically addressing differences between early and late onset UC.

PATIENTS AND METHODS

Study design

This study was designed as a single-centre, retrospective study. We enrolled 310 patients followed at the Inflammatory Bowel Diseases Clinic at our Gastroenterology and Hepatology Department during the last 6 months of 2013. The information was collected from outpatient electronic and paper written medical records and inpatient history and hospital discharge summaries.

The diagnosis of ulcerative colitis was established according current diagnostic criteria based on clinical history, associated with laboratorial, endoscopic and histological signs of inflammation of the mucosa (13). Infectious diseases were thoroughly excluded by culture and microscopic stool examination.

Patients with unclassified IBD, Crohn's disease, diverticular colitis, ischemic colitis, and primary neoplasia were excluded from the study, as were those patients with incomplete data.

Age at the date of initial diagnosis of UC was used to classify patients in two different groups: Early onset UC was considered when patients were diagnosed at the age of 40 years or before, and late onset UC, when diagnosis of UC was established after 40 years of age.

The hospital ethics committee approved the study design.

Description of variables

In this study, for each patient, several nominal variables were analysed. They were grouped in patients', disease's and treatment's related variables.

Patient related variables included age at diagnosis of UC, gender, family history of IBD (defined as having first- or second-degree relative with a history of IBD) and smoking habits (divided in current or former smoker and non-smoker).

Disease related variables involved disease duration, disease extension, disease severity, clinical course, hospitalization, and extraintestinal manifestations. Disease extension was classified according to Montreal Classification in E1 – proctitis (when mucosal changes were found in the rectum up to 15 cm from the anus), E2 – left sided UC (when mucosal changes were found up to the splenic flexure), and E3 – extensive UC (when mucosal changes were found beyond splenic flexure). Disease severity was defined by the type of treatment administered –adapted from the classification originally suggested by Loftus et al. (14) for Crohn's disease patients, but posteriorly used for UC patients (15,16)–, leading to the separation of patients in four severity grades: Mild disease (no treatment or salicylates), moderate to severe steroid-responsive disease (steroids without steroid resistance or dependence), severe steroid-refractory or steroid-dependence disease (immunesuppressors or biological agents), and medical refractory disease (submitted to surgical treatment). Clinical course was categorized in one of the four predefined patterns proposed by the IBSEN study (17) in curve 1 (remission or mild severity of intestinal symptoms after initial high activity), curve 2 (increase in the severity of intestinal symptoms after initial activity), curve 3 (chronic continuous symptoms), and curve 4 (chronic intermittent symptoms). Hospitalization was defined as admission at the hospital when patients fulfilled the Truelove and Witts' criteria for acute severe UC, as recommended by prevailing guidelines (18). Extraintestinal manifestations included joint, skin, ocular, thromboembolic or hepatobiliary manifestations of UC.

Treatment-associated variables comprised the use of topical or oral aminosalicylates, need of systemic steroids and use of immunomodulators (including azathioprine, 6-mercaptopurine, methotrexate or biological agents, namely infliximab or adalimumab).

Statistical analysis

The results were analysed using Statistical Packages for Social Sciences (SPSS) software, version 22.0 (IBM, Armonk, New York, USA). When descriptive analysis was performed, data were expressed as mean ± standard deviation for continuous variables or as absolute frequency (number) and relative frequency (percentages) for categorical variables. For comparative analysis, independent samples *t*-test, Qui-square and Fisher's exact tests were used as appropriate. Stepwise binary logistic model was performed to assess factors associated with early onset UC. Multivariable models were adjusted for potential confounding factors. Statistical significance was considered when the *p value* was less than 0.05, and all reported *P values* are two-tailed.

RESULTS

Demographic characteristics

From the patients who had been under periodic follow-up at the Inflammatory Bowel Disease Clinic of our centre, 310 patients with UC were enrolled in this study. They were purposely divided into two different groups of patients: Those with UC diagnosed at the age of 40 years or before (early onset UC) and those with an established diagnosis of UC after 40 years of age (late onset UC) (Fig. 1).

The mean age at diagnosis was 29.4 ± 6.9 years (range from 10 to 40 years) in the early onset group and 51.7 ± 8.1 years (range from 41 to 74) in the late onset group. The distribution of patients by age at diagnosis of UC was also analysed (Fig. 2).

From the 207 patients included in the early onset group, 90 patients (43.5%) were men and 117 (56.5%) were women. Conversely, the late onset group comprised 103 patients, in which 63 (61.2%) were men and 40 (38.8%)

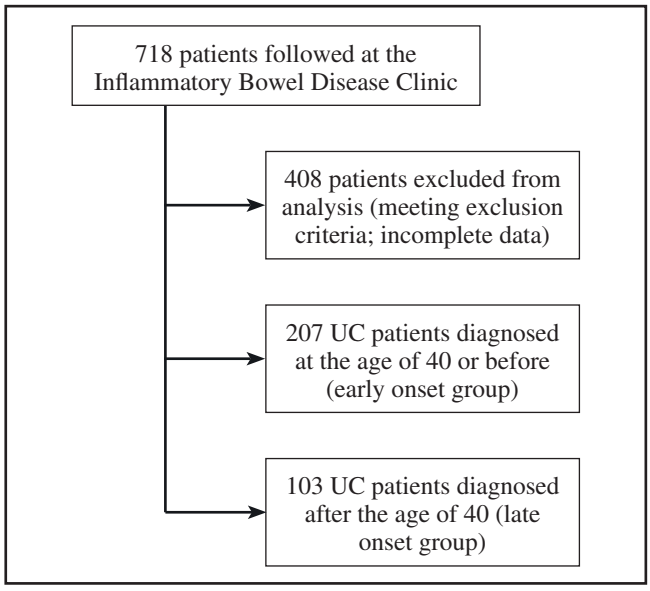

Fig. 1. Study design and patients' grouping.

were women. These differences were statistically significant (p = 0.003; OR = 1.46) (Table I). The percentage of women diagnosed with UC is higher than men's in the first decades of life. However, as time goes by, a diagnosis of UC is increasingly established in men and less frequently in women (Fig. 3). The male to female ratio was 1:1.3 in the younger group and 1.6:1 in the older group.

All the analysed patients in our series were Caucasian.

Regarding family history of IBD, 14 (6.8%) out of 207 patients diagnosed before the age of 40 years had at least one first- or second-degree relative with IBD. On the other hand, only 4 (3.8%) out of 103 patients diagnosed later in life had an affected relative. There were no significant differences between the two groups (p = 0.44).

In relation to smoking habits, 45 (21.7%) patients in the early onset group and 27 (26.2%) patients in the late onset group were current or former smokers. Once again no significant differences were found between groups (p = 0.38).

Table I. Demographic characteristics: Comparison between patients with early onset and late onset UC

	Early onset (n = 207)	*Late onset (n = 103)*	*p value*
Gender – no. (%)			
Male	90 (43.5)	63 (61.2)	0.003*
Female	117 (56.5)	40 (38.8)	
Family history – no. (%)			
Yes	14 (6.8)	4 (3.8)	0.44
No	193 (92.2)	99 (96.2)	
Smoking – no. (%)			
Current or former smoker	45 (21.7)	27 (26.2)	0.38
Non-smoker	162 (78.3)	76 (73.8)	

Characteristics of the disease

Before proceeding further analysis, we confirmed that there were no differences in disease's duration between both groups. In fact, the mean duration of disease in the younger group was 9.8 ± 7.5 years, while in the older group it was 8.4 ± 6.1 years. These differences were not significant (p = 0.098) (Table II).

Extension and severity of the disease, clinical course, need of hospital admission for acute severe exacerbation and extraintestinal manifestations were then analysed.

In the early onset group, 75 (36.2%) patients had isolated proctitis, 70 (33.8%) patients had left sided colitis, and 62 (30.0%) had extensive colitis. Similarly, in the late onset group, 40 (38.8%) patients had proctitis, 39 (37.9%) had left sided colitis, and 24 (23.3%) had extensive colitis. No differences were found between the two groups regarding this topic (p = 0.46).

Regarding the severity of the disease, 105 (50.7%) patients with early onset UC had mild disease, 52 (25.1%) had moderate to severe steroid-responsive disease, and 50 (24.2%) had severe steroid-refractory or steroid-de-

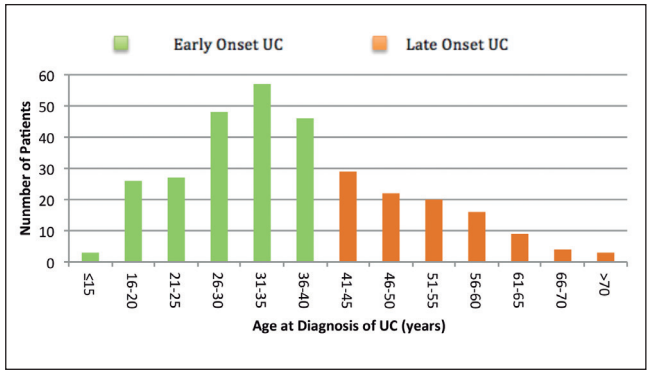

Fig. 2. Age distribution of patients according to the age at diagnosis of UC.

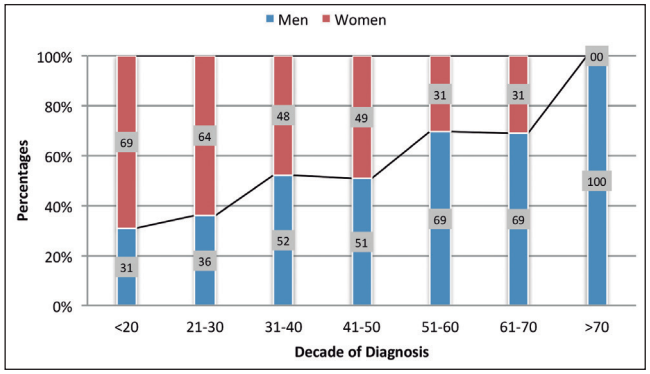

Fig. 3. Percentage of men and women in each decade of diagnosis.

Table II. Disease's characteristics: Comparison between patients with early onset and late onset UC

	Early onset (n = 207)	*Late onset (n = 103)*	*p value*
Duration (years ± SD[2])			
9.8 ± 7.5	8.4 ± 6.1		0.098
Extension – no. (%)			
Proctitis (E1)	75 (36.2)	40 (38.8)	0.46
Left sided colitis (E2)	70 (33.8)	39 (37.9)	
Extensive colitis (E3)	62 (30.0)	24 (23.3)	
Severity – no. (%)			
Mild	105 (50.7)	73 (70.9)	
Moderate to severe steroid-responsive	52 (25.1)	17 (16.5)	0.003*
Severe steroid-dependent or steroid-refractory	50 (24.2)	13 (12.6)	
Medical refractory	0 (0.0)	0 (0.0)	
Clinical course – no. (%)[1]			
Curve 1	110 (53.1)	69 (66.9)	
Curve 2	19 (9.2)	12 (11.7)	0.026*
Curve 3	26 (12.6)	10 (9.7)	
Curve 4	52 (25.1)	12 (11.7)	
Hospitalization – no. (%)			
Yes	60 (29.0)	12 (11.7)	0.001*
No	147 (71.0)	91 (88.3)	
Extraintestinal manifestations – no. (%)			
Yes	32 (15.5)	13 (12.6)	0.50
No	175 (84.5)	90 (87.4)	

[1]According to IBSEN Study (17): curve 1 (remission or mild severity of intestinal symptoms after initial high activity), curve 2 (increase in the severity of intestinal symptoms after initial activity), curve 3 (chronic continuous symptoms), and curve 4 (chronic intermittent symptoms). [2]Standard deviation.

pendence disease. On the contrary, in the late onset UC group, 73 (70.9%) patients had mild disease, 17 (16.5%) had moderate to severe steroid-responsive disease, and 13 (11.6%) had severe steroid-refractory or steroid-dependence disease. Only 1 patient (1%) had a colectomy performed, which indication was dysplasia and not medical refractory disease. These differences were statistically significant (p = 0.003).

Concerning the clinical course of the disease, four different curves of disease activity were considered, as described in methods. In those patients diagnosed at or before the age of 40 years, 110 (53.1%) had remission or mild severity of symptoms after initial high activity (curve 1), 19 (9.2%) showed increase in the severity of symptoms after initial low activity (curve 2), 26 (12.6%) referred chronic continuous symptoms (curve 3), and 52 (25.1%) patients had chronic intermittent symptoms (curve 4). On the other hand, from those patients diagnosed with UC after the age of 40 years, 69 (66.9%) had their disease course represented in curve 1, 12 (11.7%) in curve 2, 10 (9.7%) in curve 3 and 12 (11.7%) in curve 4. Comparative analysis showed again significant differences (p = 0.026).

The need of hospitalization, when patients fulfilled the Truelove and Witts' criteria for severe acute colitis, was another studied topic. In the early onset UC group, 60 patients (29%) required hospitalization; alternatively, in the late onset UC group, only 12 patients (11.7%) needed hospital admission (p = 0.001; OR = 2.49).

When extraintestinal manifestations were evaluated, we found that 32 patients (15.5%) in the early onset UC group had at least another affected organ: 24 patients had arthritis, 5 patients had skin conditions (1 pyoderma gangrenosum and 4 erythema nodosum), and 3 had episcleritis. On the other hand, in the late onset group, only 13 patients (12.6%) had extraintestinal involvement: 10 patients had arthritis, 2 had history of thromboembolic events, and 1 had episcleritis. These findings were not significantly different between the two groups of patients (p = 0.50).

Characteristics of the treatment

All the patients included in our study required topical aminosalicylates at some time during the clinical course of the disease, independently of the age of onset of symptoms.

When the use of oral aminosalicylates was analysed, we verified that 194 patients (93.7%) in the early onset UC group have used them *versus* 89 patients (86.4%) in the late onset UC group (p = 0.032; OR = 1.09) (Table III).

Regarding the use of systemic steroids for the treatment of colorectal inflammation, it was required in 97 patients (46.9%) in the early onset UC group *versus* only 30 patients (29.1%) in the late onset UC group (p = 0.003; OR = 1.61).

Finally, we evaluated the use of immunomodulators in both groups. In the early onset UC group, 49 patients (23.7%) needed azathioprine or 6-mercaptopurine, whereas only 12 patients (11.7%) in the late onset UC needed this type of medical therapy. Additionally, 15 patients (7.2%) in the early onset UC group required treatment with biological agents (13 infliximab and 2 adalimumab), while 6 patients (5.8%) in the late onset UC group used anti-TNF agents (all of them used infliximab). Although the use of thiopurines was significantly more common in the early onset UC group (p = 0.012; OR = 2.03), differences between groups regarding the use of biological agents were not statistically significant (p = 0.64).

Table III. Treatment's characteristics: Comparison between patients with early onset and late onset UC

	Early onset (n = 207)	*Late onset (n = 103)*	*p value*
Oral aminosalicylates – no. (%)	194 (93.7)	89 (86.4)	0.032*
Systemic steroids – no. (%)	97 (46.9)	30 (29.1)	0.003*
Thiopurines – no. (%)	49 (23.7)	12 (11.7)	0.012*
Biological agents – no. (%)	15 (7.2)	6 (5.8)	0.64

Factors associated with early onset UC

Stepwise binary logistic model was performed to assess factors associated with early onset UC.

Potential confounding factors that were adjusted for in the multivariate analysis included the gender of the patient, the severity and clinical course of the disease, the need of hospitalization, and the use of oral aminosalicylates, systemic steroids or thiopurines.

Multivariate analysis revealed that female gender (OR 1.77; 95% CI 1.08-2.91), chronic intermittent clinical course (OR 2.89; 95% CI 1.46-5.72), and need of hospitalization (OR 2.34; 95% CI 1.17-4.70) were associated with early onset of UC (Fig. 4). In other words, when UC is diagnosed before the age of 40 years, there are 77% more chances for the disease to affect a woman than a man. Also, a patient with early onset UC has 2.34 more chances of requiring hospitalization than a patient diagnosed after the 40 years old. Finally, early onset UC patients have 2.89 more chances of developing chronic intermittent symptoms than patients with late onset UC.

In the performed analysis, severity of the disease, and use of oral aminosalicylates, systemic steroids or thiopurines were not associated with this earlier form of the disease.

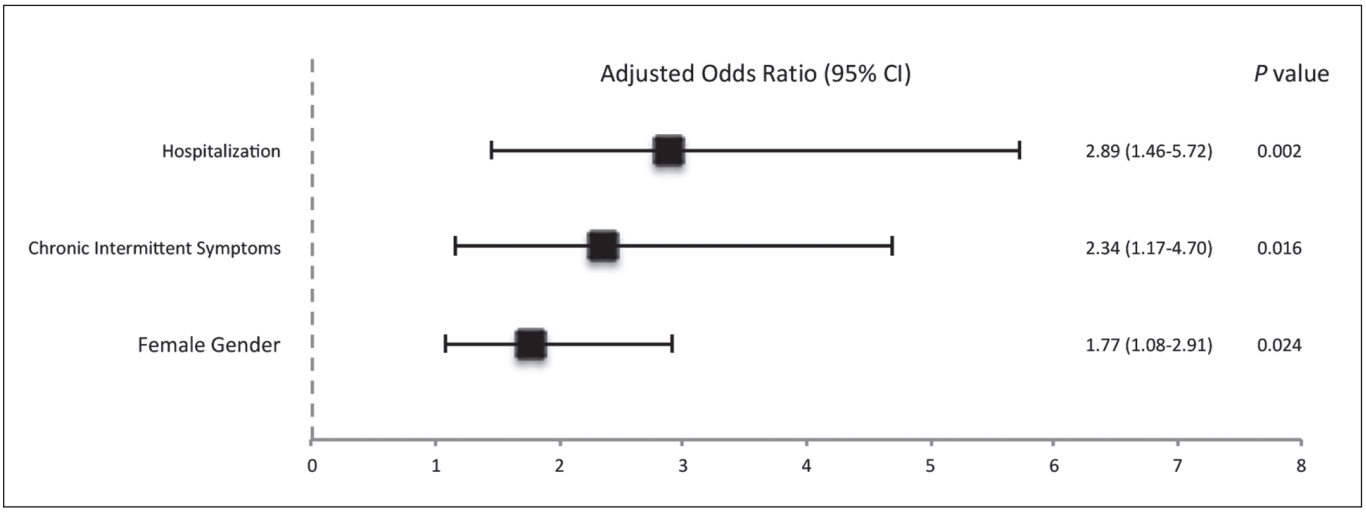

Fig. 4. Odds ratio for early onset UC.

DISCUSSION

Being a heterogeneous disease by itself, UC is further diversified by genetic background, environmental factors and gut microbiota, which vary among different populations. Thus, the recognition of features of the disease in specific populations is of major importance when an improved and individualized treatment is to be achieved. As the incidence of UC seems to be increasing and the world population is ageing, it is appropriate to expect a growing number of patients being diagnosed with UC in later decades of life. While some studies describing specific demographic and clinical characteristics of Portuguese patients with UC have been published (15,16), studies specifically addressing the differences between Portuguese patients with early and late onset UC are lacking.

The concepts of early and late onset UC have been inconsistently defined in the literature. While some authors defined early onset UC when diagnosis was established anytime between the age of 0-20 years (3,19-21), and late onset UC when disease was identified after the age of 60-95 (19,22-24) other studies commonly consider the age of 40 years old a reasonable cut-off point (25). In fact, according to the World Health Organization, the transition from early adulthood and late adulthood occurs when individuals reach 40 years old. Even more important is the fact that Viena Classification and, more recently, Montreal Classification, commonly used to classify Crohn's disease patients, use that same cut-off point when defining different groups of patients (26). Bearing these facts in mind, and as in our group of patients only six were diagnosed before or at the age of 16 years, it seemed legitimate to group our patients in the previous defined groups: Early onset UC when disease was identified before or at the age of 40 years old and late onset UC when disease was diagnosed later in life.

Although not completely understood, the impact of age at diagnosis in the natural history and features of UC can be better explained when genetic influences, environmental factors, gut microbiota composition and immune responses according to age are taken into consideration.

The role of genetic factors in early onset UC is thought to be greater than in late onset disease when family history of IBD is analysed. In our study, despite no statistical significance was reached, family history of IBD was almost double in the early onset group than in the late onset group, which is concordant with other previous studies (7,23,27). The link between genetic influences and onset of UC is further strengthened by genome-wide association studies, which have identified at least 23 specific gene polymorphisms associated with a higher susceptibility of developing UC (28). Some of those genes, namely multidrug-resistant transporter 1 (*MDR1*) gene, important for the barrier function of the intestinal epithelium, were associated with a younger age of onset and a more severe course of disease (28). Regarding genetic influence on age of onset, and according to our results, we can further presume that female gender is more frequently associated with early onset disease, while male gender seems to predispose to late onset UC, which is accordant with other previous studies (2,23,27).

Though with variable degree of evidence, different environmental factors, such as smoking, nonsteroidal anti-inflammatory drugs, prior appendectomy, previous antibiotic use and urbanization, have been related to IBD expression and age of onset of the disease (29). In the current study, only smoking status was analysed between groups. Previous studies have reported the protective effect of active smoking on the development and clinical course of UC (30,31). As shown in our results, smoking habits do not seem to influence the age of onset of the disease. However, these results need to be interpreted carefully because no distinction between current and former smokers was made.

Recent reviews confirm the major role of altered bowel microbiota in the pathogenesis of IBD, namely in UC (32,33). Nevertheless, the knowledge of how dysbiosis can influence the age of onset is still scarce. Despite not being the purpose of the current study, we can hypothesize that the impact of dysbiosis on the age of onset of UC, if any, would probably be more notorious in older patients, in whom changes in nutrition, living conditions, motility and gut immune function or previous antibiotic exposure that can modify gut microbiota are likely.

The effect of ageing in the immune system and in inflammatory processes, namely on UC, as well as the way they clinically manifest are far from being completely understood. Nonetheless, evidence suggests that immune senescence present in older patients may be characterized by less-robust immune responses, which may influence UC behaviour, namely disease extension, severity and clinical course (7). The impact of age of onset on disease extension is not consensual between studies. While some studies, similarly to our results, found no significant differences in disease extension between early and late onset UC (7,22,27), other found that UC diagnosed in younger patients is associated with a more extensive disease and even with a higher probability of disease extension (24,29). Another aspect that is believed to be influenced by the age of diagnosis is disease severity. Even though we have not used Montreal Classification for evaluate disease severity and thus direct comparison between studies is limited, we showed that, when diagnosed at younger ages, patients should expect a more severe disease. In fact, in the early onset group, nearly a quarter of patients were steroid-dependent or steroid-refractory, requiring more aggressive medical therapies such as thiopurines or biologic agents. On the other hand, in the late onset group, approximately three quarters of patients had mild disease and only a minority had a more severe disorder. Moreover, severe exacerbation of disease needing hospitalization was also significantly more common in the early onset group. Regarding clinical course, a chronic intermittent disease

was significantly more common in younger patients, while older patients were more prone to be in remission or have mild symptoms after initial high activity. How immune system can exactly influence the occurrence of extraintestinal manifestations at difference ages of diagnosis is still unknown. In fact, while some authors report them more frequently when diagnosis is made earlier in life (15,23), other describe a higher incidence in older patients (34). In this study, no significant differences were found between patients.

Although some specific guidelines for the paediatric population exist (35), there are no distinct guidelines for the treatment of adults diagnosed before or after the age of 40 years old. In fact, in both groups, medical management should be equally guided by location, extension and severity of the disease (36). As it is the current first-line treatment, topical aminosalicylates have been used in all the patients included in our series. However, the use of more intensive medical therapy was significantly different between groups, specifically oral aminosalicylates, systemic steroids and thiopurines, which were used more commonly in the early onset of disease group. The necessity of more aggressive medical therapy in patients diagnosed earlier in life has been matter of debate. While some studies report results similar to the ones we achieved (37), other reported no distinctions among groups (7,22). Less expectedly, but as shown by some previous studies (7,22), we confirmed no differences regarding anti-TNF agents use between both groups. This result should however be interpreted cautiously due to the reduced number of patients on biologic treatment in our series. Contrasting with the majority of other studies who report variable percentages of patients, either with early or late onset of disease, requiring colectomy with ileal pouch-anal anastomosis, our group of patients present only one in which colectomy was need for treatment of dysplasia and thus comparative analysis was not possible. Although some studies report higher colectomy rates in patients with early onset disease (27), most studies agree that no differences in the rate of colectomy exist between early and late onset UC (7,15,22,37).

In conclusion, this is the first single-centre published study focusing in differences between early and late onset UC, diagnosed in a Portuguese northern population. When diagnosed before the age of 40-years-old, UC preferably affects women and has a more severe disease, with more frequent hospitalizations and chronic intermittent symptoms. On the contrary, UC diagnosed after the 40-years-old, tends to affect primarily men, with a more indolent clinical course, requiring less hospitalizations. This fact might have implications in planning timely and individualized future therapeutic strategies.

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